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<p>(21) International Application Number: PCT/US93/03716 (22) International Filing Date: 20 April 1993 (20.04.93) (30) Priority data: 07/871,558 20 April 1992 (20.04.92) US (71) Applicant: MEDLOGIC, INC. [US/US]; 1223-B Lake Plaza Drive, Colorado Springs, CO 80906 (US). (72) Inventor: BARLEY, Leonard, V., Jr.; 65 Kirkstone, Colorado Springs, CO 80906 (US). (74) Agent: KREBS, Robert, E.; Burns, Doane, Swecker & Mathis, George Mason Building, Washington and Prince Streets, P.O. Box 1404, Alexandria, VA 22313-1404 (US).</p> <div data-bbox="358 842 699 1020" style="border: 1px solid black; padding: 5px; margin-top: 20px;"><p>LEE HOLME PATENT A/S</p><p>Bill of</p><p>Exhibit: <i>2701</i></p></div>		<p>(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>-With international search report.</i></p>
<p>(54) Title: METHODS FOR RETARDING BLISTER FORMATION BY USE OF CYANOACRYLATE ADHESIVES</p> <p>(57) Abstract</p> <p>A cyanoacrylate adhesive is applied to the skin areas prone to blistering either prior to or during physical activities but prior to blister formation.</p>		

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**METHODS FOR RETARDING BLISTER FORMATION
BY USE OF CYANOACRYLATE ADHESIVES**

BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention is directed to methods for retarding blister formation by use of cyanoacrylate adhesives that can be applied to skin areas prone to blistering prior to blister formation.

State of the Art

10 Cyanoacrylate adhesives have been suggested for a variety of adhesive purposes including glues and surgical adhesives. In particular, cyanoacrylate adhesives of formula I:



wherein R is an alkyl or other suitable substituents
20 are disclosed in U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826. Typically, when used as adhesives for living tissues, the R substituent is alkyl of from 2 to 6 carbon atoms and most often is butyl.

25 The suggested medical uses for cyanoacrylate adhesives have been limited to surgical environments wherein the cyanoacrylate adhesives are utilized as an alternative to sutures and are employed in a sterile environment. Specifically, in surgical environments,
30 the cyanoacrylate adhesive is applied to separate sections of soft tissue. The cyanoacrylate adhesive,

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in the presence of water found in soft tissue, bonds to the skin as well as polymerizes so as to join separate sections of soft tissue together.

SUMMARY OF THE INVENTION

5 The present invention, generally speaking, is a result of the discovery that application of cyanoacrylate adhesives to blister prone areas and subsequent polymerization results in the formation of an artificial callus over the blister prone area
10 thereby retarding the formation of blisters in these areas. More particularly, the application of cyanoacrylate adhesives is only to the surface of the skin and not to cut areas of skin.

 Thus, it can be understood that the present
15 invention is directed to methods for inhibiting blister formation by application of a cyanoacrylate adhesive to the skin area prone to blistering prior to blister formation. Accordingly, in one of its method aspects, the present invention is directed to a method for
20 inhibiting blister formation arising from friction during physical activities which method comprises:

 applying, either prior to or during physical activities but prior to blister formation, a quantity of cyanoacrylate adhesive to a surface area of uncut
25 skin which is prone to blister formation, which quantity of cyanoacrylate adhesive is sufficient to form an artificial callus; and

 maintaining the cyanoacrylate adhesive under conditions which polymerize the adhesive thereby
30 forming an artificial callus which adheres to the surface area of uncut skin where the adhesive was applied,

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wherein the cyanoacrylate, in monomeric form,
is represented by formula I:



where R is selected from the group consisting of alkyl
of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon
atoms, cycloalkyl groups of from 5 to 8 carbon atoms,
phenyl, 2-ethoxyethyl, 3-methoxybutyl, and
a substituent of the formula:



where each R' is independently selected from the group
consisting of hydrogen and methyl and R'' is selected
from the group consisting of alkyl of from 1 to 6
carbon atoms; alkenyl of from 2 to 6 carbon atoms;
alkynyl of from 2 to 6 carbon atoms; cycloalkyl of from
3 to 8 carbon atoms; aralkyl selected from the group
consisting of benzyl, methylbenzyl and phenylethyl;
phenyl; and phenyl substituted with 1 to 3 substituents
selected from the group consisting of hydroxy, chloro,
bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy
of from 1 to 4 carbon atoms.

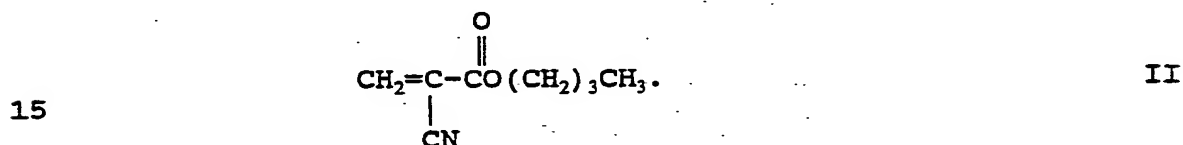
Preferably R is alkyl of from 1 to 10 carbon
atoms and more preferably alkyl of from 2 to 6 carbon
atoms. Most preferably, R is n-butyl.

In another of its method aspects, the present
invention is directed to a method for inhibiting
blister formation arising from friction during physical
activities which method comprises:

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applying, either prior to or during physical activities but prior to blister formation, at least 0.02 milliliter (ml) of cyanoacrylate adhesive per square centimeter of surface area of uncut skin which is prone to blister formation; and

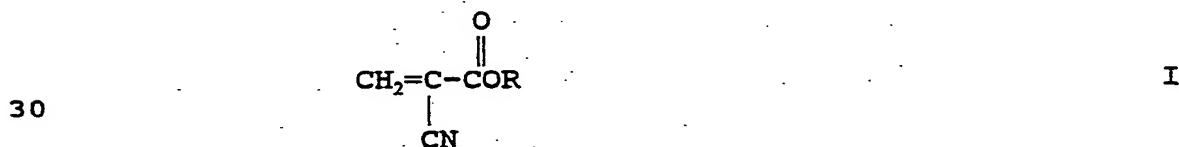
maintaining the cyanoacrylate adhesive under conditions which polymerize the adhesive thereby forming an artificial callus which adheres to the surface area of uncut skin where the adhesive was applied wherein the cyanoacrylate, in monomeric form, is represented by formula II:



In a preferred embodiment, the cyanoacrylate adhesive to be applied to the skin has a viscosity of from about 2 to about 1000 centipoise at 20°C. More preferably, the cyanoacrylate adhesive is in monomeric form and has a viscosity of from about 2 to about 20 centipoise at 20°C.

As used herein, the following terms have the following meanings:

The term "cyanoacrylate adhesive" refers to adhesives based on cyanoacrylate monomers of formula I:



where R is selected from the group consisting of alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms, cycloalkyl groups of from 5 to 8 carbon atoms,

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phenyl, 2-ethoxyethyl, 3-methoxybutyl, and a substituent of the formula:



where each R' is independently selected from the group consisting of hydrogen and methyl and R'' is selected
 10 from the group consisting of alkyl of from 1 to 6 carbon atoms; alkenyl of from 2 to 6 carbon atoms; alkynyl of from 2 to 6 carbon atoms; cycloalkyl of from 3 to 8 carbon atoms; aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl;
 15 phenyl; and phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

Preferably, R is an alkyl group of from 1 to
 20 10 carbon atoms including methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, iso-pentyl, n-hexyl, iso-hexyl, 2-ethylhexyl, n-heptyl, octyl, nonyl, and decyl. More preferably, R is butyl and most preferably, R is n-butyl.

25 These cyanoacrylate adhesives are known in the art and are described in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826.

The term "artificial callus" refers to a
 30 layer of polymerized cyanoacrylate adhesive formed over and strongly adhering to a defined surface area of skin.

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The term "blister" refers to an elevation of the epidermis containing a watery liquid which arises from friction during physical exertion as opposed to some type of disease condition (e.g., chicken pox).

5 Contrarily, the term "blister" does not refer to irritated skin areas which have not yet blistered (i.e., formed a watery liquid under the epidermis). In this invention, the cyanoacrylate adhesive can be applied to irritated skin areas prior to blister
10 formation as a means for preventing further irritation and, thereby, for retarding blister formation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The cyanoacrylate adhesive to be applied onto the skin can be monomeric or partially polymeric. In
15 general, partially polymerized cyanoacrylate adhesives are liquid polymers having a higher viscosity than that of the corresponding monomer and, therefore, are better suited for those applications which are intended to be specific for a particular skin area. In other words,
20 less viscous materials are more likely to "run" (i.e., flow) into areas where application was not intended.

The cyanoacrylate adhesives used herein preferably have a viscosity of from about 2 to about 1000 centipoise and more preferably from about 2 to
25 about 20 centipoise at 20°C. The specific viscosity of the formulation depends on the amount and degree of partially polymerized cyanoacrylate adhesive employed. Such factors are readily ascertainable by the skilled artisan. For example, methods for preparing partially
30 polymerized cyanoacrylate adhesives are disclosed, for example, by Rabinowitz, U.S. Patent No. 3,527,224.

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Monomeric forms of cyanoacrylate adhesives are often preferred where application is to be made to a large surface. This preference results from the fact that those forms are less viscous and, accordingly, will permit more facile large surface area application. Mixtures of monomeric forms of cyanoacrylate adhesive and partially polymerized forms of cyanoacrylate adhesive can also be used to prepare a formulation having intermediate viscosities.

Upon contact with skin moisture, the cyanoacrylate adhesives will polymerize or, in the case of partially polymerized cyanoacrylate adhesives, will further polymerize, at ambient conditions (skin temperature) over 10 seconds to 60 seconds to provide for a solid layer which forms over and strongly adheres to the surface of the skin. This polymer layer serves as an artificial callus and protects the underlying skin against blistering in much the same way as does a natural callus.

The artificial callus, because of its strong binding affinity to skin and because of the durability of the polymerized cyanoacrylate adhesive serves as a substitute for human calluses.

In general, sufficient cyanoacrylate adhesive is applied onto the surface of the skin to provide for an artificial callus having sufficient thickness to inhibit blister formation. In a preferred embodiment, the artificial callus has a thickness of at least about 0.1 millimeter (mm) and more preferably at least about 0.3 mm. In another preferred embodiment, the artificial callus has a thickness ranging from about 0.1 mm to about 0.5 mm and even more preferably from about 0.1 to 0.3 mm. Normally, thicknesses greater

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than about 0.5 mm are not preferred because shearing forces may disrupt the adhesive formed.

In another preferred embodiment, the artificial callus is preferably formed by application of at least 0.02 ml of cyanoacrylate adhesive per square centimeter of skin.

Various parts of the human body are prone to blister formation, including the grip portions of hands and the base of feet. During physical exertion, these parts of the body can be subject to friction by such activities as walking/jogging (feet), shoveling (hands). The all too familiar result of such activities, particularly in people not accustomed to such activities, is the formation of blisters in those areas prone to blister formation.

Formulations

The cyanoacrylate adhesive formulations employed herein generally comprise monomeric and/or partially polymerized compounds of formula I described above. These compositions are liquid in nature and upon contact with skin moisture will polymerize to provide a solid film or layer over the skin surface.

The formulations may additionally contain one or more optional additives such as colorants, perfumes, and stabilizers. In practice, each of these optional additives should be both miscible and compatible with the cyanoacrylate adhesive. Compatible additives are those that do not prevent the use of the cyanoacrylate adhesives for their intended use.

In general, colorants are added so that the polymerized film will contain a discrete and

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discernable color. Perfumes are added to provide a pleasant smell to the formulation. Stabilizers are added to minimize in situ polymerization in containers during storage. Each of these additives are
5 conventional. For example, suitable stabilizers are disclosed in U.S. Patent No. 4,650,826.

The formulation is generally stored in an applicator for use in a single dose application or for use in repeated applications. Single dose applicators
10 include those having breakable or removable seals that prevent moisture, including atmospheric moisture, from contacting the formulation and causing in situ polymerization.

For repeated and intermittent usage, minimal
15 exposure to atmospheric moisture is required. This can be achieved by devices having very narrow outlets and low initial deadspace. One applicator for such repeated intermittent use is described in U.S. Patent No. 4,958,748.

20 In applicators suitable for repeated intermittent uses, the cyanoacrylate adhesive is stored at ambient conditions and is selected to be bacteriostatic. See, for example, Rabinowitz et al., U.S. Patent No. 3,527,224. When the selected adhesive is
25 bacteriostatic, prolonged storage at ambient conditions is without regard to the sterility of the formulation because there is no adverse build-up of bacteria during storage.

Methodology

30 The above-described formulations are applied onto the skin surface area under conditions suitable for polymerizing the adhesive so as to form an

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artificial callus. In general, sufficient amounts of cyanoacrylate adhesive are employed to permit formation of an artificial callus having a sufficient thickness to inhibit blister formation. In a preferred
5 embodiment, the artificial callus has a thickness of at least about 0.1 mm and more preferably at least about 0.3 mm. Such artificial calluses are formed by applying at least about 0.02 ml of cyanoacrylate adhesive per square centimeter of skin surface area and
10 preferably from about 0.02 ml to about 0.5 ml of cyanoacrylate adhesive per square centimeter of skin surface area.

In another preferred embodiment, the amount of cyanoacrylate adhesive employed does not exceed
15 about 0.05 ml per square centimeter. At concentrations in excess of the maximum preferred concentration, it can, in some cases, take too long for the artificial callus to form, and the resulting callus is subject to shear forces. Additionally, higher concentrations of
20 adhesive create polymers having less than desirable skin adherence and durability characteristics.

The amount of cyanoacrylate adhesive applied onto the skin surface area can be controlled by the amount of adhesive packaged in a single dose product or
25 by use of a multiple use dispenser which governs the amount of material applied onto the skin. In this regard, the dispenser described by Otake, U.S. Patent No. 4,958,748 is particularly advantageous because it dispenses the adhesive in a controlled drop-wise
30 manner.

For inhibiting the formation of blisters, the cyanoacrylate adhesive is applied prior to blister formation. That is, the cyanoacrylate adhesive is

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applied onto the blister prone areas of the skin prior to initiation of physical activity which would be expected to result in the formation of blisters. Additionally, the cyanoacrylate adhesive can be applied
5 onto blister prone areas at some point during physical activity when blister prone areas begin exhibiting some of the classic signs of blister formation (i.e., irritation, perceived heat and so forth).

Upon application of the cyanoacrylate
10 adhesive, the surface skin moisture and temperature are sufficient to initiate polymerization of the adhesive upon application. Thereafter, the skin surface is maintained under suitable conditions to allow polymerization to proceed to formation of an artificial
15 callus.

In general, the particular length of time required for polymerization will vary depending upon factors such as the amount of adhesive applied, the temperature of the skin, the moisture content of the
20 skin and the like. However, in a preferred embodiment, polymerization is generally complete within about 10 to about 60 seconds while the skin is maintained at ambient conditions. During this period, the person to whom application of the cyanoacrylate adhesive has been
25 made merely allows the adhesive to form a callus while minimizing any action to prevent the adhesive from being dislodged from that portion of the skin where it was applied (e.g., washing his hands, placing socks on his feet) or to adhere to unintended objects (e.g.,
30 gripping an object immediately after application of the adhesive). After the artificial callus has formed, the callus strongly adheres to the skin, is flexible and waterproof thereby permitting the person to conduct the intended activity.

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In general, the artificial callus will adhere to the skin for a period of about 2-3 days after which time it sloughs off. However, if it is desirable to remove the artificial callus prior to its sloughing off, the artificial callus can be removed with acetone (nail polish remover).

It can now be understood that the methods of this invention are useful in retarding the formation of blisters. In particular, the methods of this invention result in the formation of artificial calluses which inhibit blister formation. As such, the methods of this invention are particularly suited for retarding blister formation in people who are prone to blister formation.

The following example illustrates certain embodiments of the invention but is not meant to limit the scope of the claims in any way.

Example 1

A cyanoacrylate adhesive formulation was prepared in monomeric form using n-butyl α -cyanoacrylate of formula II above. The formulation was placed into the dispensing device described by Otake, U.S. Patent No. 4,958,748. Three drops of the formulation were placed drop-wise onto the palm of the hand in an area prone to blister formation of about 2 square centimeters in area so as to provide about 0.02 ml of adhesive per square centimeter. The hand was held palm up for about 1 minute. At this time an artificial callus had formed over this surface.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such

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modifications coming within the scope of the appended claims are intended to be included therein.

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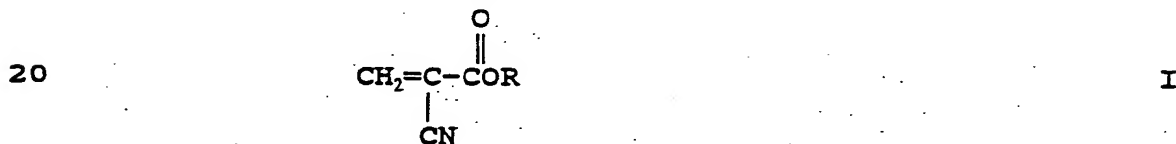
WHAT IS CLAIMED IS:

1. A method for inhibiting blister formation arising from friction during physical activities which method comprises:

5 applying, either prior to or during physical activities but prior to blister formation, a quantity of cyanoacrylate adhesive to a surface area of uncut skin which is prone to blister formation, which quantity of cyanoacrylate adhesive is sufficient to
10 form an artificial callus; and

maintaining the cyanoacrylate adhesive under conditions which polymerize the adhesive thereby forming an artificial callus which adheres to the surface area of uncut skin where the adhesive was
15 applied;

wherein the cyanoacrylate, in monomeric form, is represented by formula I:



where R is selected from the group consisting of alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon
25 atoms, cycloalkyl groups of from 5 to 8 carbon atoms, phenyl, 2-ethoxyethyl, 3-methoxybutyl, and a substituent of the formula:



where each R' is independently selected from the group consisting of hydrogen and methyl and R'' is selected
35 from the group consisting of alkyl of from 1 to 6 carbon atoms; alkenyl of from 2 to 6 carbon atoms;

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alkynyl of from 2 to 6 carbon atoms; cycloalkyl of from 3 to 8 carbon atoms; aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl; phenyl; and phenyl substituted with 1 to 3 substituents
5 selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

2. A method according to Claim 1 wherein R is alkyl of from 2 to 6 carbon atoms.

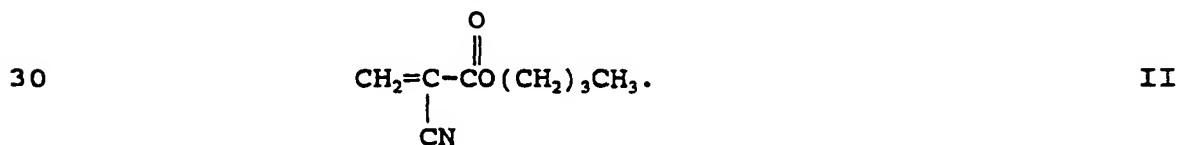
10 3. A method according to Claim 2 wherein R is butyl.

4. A method according to Claim 3 wherein R is n-butyl.

15 5. A method for inhibiting blister formation arising from friction during physical activities which method comprises:

applying, either prior to or during physical activities but prior to blister formation, at least 0.02 ml of cyanoacrylate adhesive per square centimeter
20 of surface area of uncut skin which is prone to blister formation; and

maintaining the cyanoacrylate adhesive under conditions which polymerize the adhesive thereby forming an artificial callus which adheres to the
25 surface area of uncut skin where the adhesive was applied wherein the cyanoacrylate, in monomeric form, is represented by formula II:



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6. The method according to Claim 1 wherein the cyanoacrylate adhesive has a viscosity of from about 2 to about 1000 centipoise at 20°C.

5 7. The method according to Claim 6 wherein the cyanoacrylate adhesive has a viscosity of from about 2 to about 20 centipoise at 20°C.

8. The method according to Claim 5 wherein the cyanoacrylate adhesive has a viscosity of from about 2 to about 1000 centipoise at 20°C.

10 9. The method according to Claim 8 wherein the cyanoacrylate adhesive has a viscosity of from about 2 to about 20 centipoise at 20°C.

15 10. The method according to Claim 1 wherein the cyanoacrylate adhesive is applied at a concentration of at least 0.02 ml per square centimeter of surface area of uncut skin.

20 11. The method according to Claim 5 wherein the cyanoacrylate adhesive is applied at a concentration of from about 0.02 ml to about 0.05 ml per square centimeter of surface area of uncut skin.

12. The method of Claim 10 wherein the cyanoacrylate adhesive is applied at a concentration of from about 0.02 ml to about 0.05 ml per square centimeter of surface area of uncut skin.

25 13. The method of Claim 1 wherein the cyanoacrylate adhesive is polymerized by maintaining the cyanoacrylate adhesive on the uncut skin surface for a period of from about 10 to 60 seconds and at ambient skin temperature.

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14. The method of Claim 5 wherein the
cyanoacrylate adhesive is polymerized by maintaining
the cyanoacrylate adhesive on the uncut skin surface
for a period of from about 10 to 60 seconds and at
5 ambient skin temperature.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/03716

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/78; A61L 25/00

US CL : 424/78.35; 602/52, 904; 128/893

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/78.35; 602/52, 904; 128/893; 526/298; 523/111

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Archives of Dermatology, Vol. 107, 1973, (AKERS), "Treating Friction Blisters With Alkyl-alpha-Cyanoacrylates", pages 544-547.	1-14

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be part of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "G" document member of the same patent family
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Date of the actual completion of the international search

18 JUNE 1993

Date of mailing of the international search report

03 AUG 1993

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